(11)

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Complete Specification entitled (54) TRIFLUOROMETHYLPHENYL PIPERAZINE DERIVATIVES AS ANORECTIC AGENTS

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Related Art (58) Nil

The following statement is a full description of this invention, including the best method of performing it known to us :

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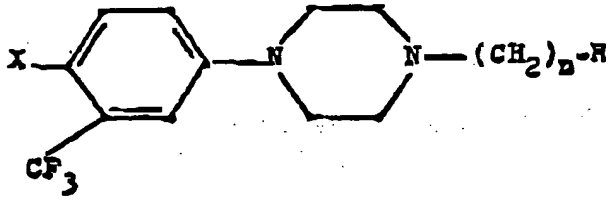
L239-42-N.D.-1 P.C.

45940/92

The invention relates to compounds having anorectic properties and is particularly concerned with a class of novel 1-(3-trifluoro-methyl-phenyl)-4-(cyclic-amido-alkyl)-piperazines which show anorectic properties with good duration of action and little or no central nervous system or cardiovascular activity, and show little tendency towards the development of drug tolerance. The compounds are therefore particularly useful in combatting a tendency towards obesity by reducing appetite in human subjects.

The compounds of the present invention are compounds of the general formula:



I

where R represents a succinimido, glutarimido, 2,4-dioxo-1(or 3)-imidazolidinyl or 2,4-dioxo-1(or 3)-hexahydropyrimidinyl group, the last two groups being optionally substituted on the imino nitrogen atom with a methyl or an ethyl group;

X represents a hydrogen, fluorine, chlorine or bromin at m;

and n is 2 or 3;

and the non-toxic acid additi n salts or such compounds.

Non-t xic acid addition salts of the compounds f

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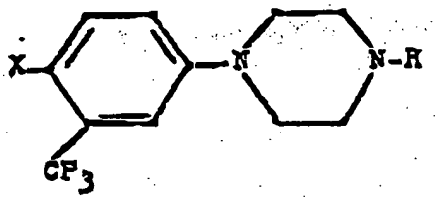
the invention can be prepared from acids which form addition salts containing non-toxic anions, such as the hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate, saccharate, and p-toluene sulphonate salts.

The compounds of the invention may be prepared in a number of ways:

(1) A 1-aryl-piperazine of the formula:



(II)

is reacted with an ω-R-substituted alkyl halide of the formula: hal-$(CH_2)_n$-R, where hal represents a halogen atom, preferably a chlorine or a bromine atom, by heating in a dry inert organic solvent, e.g. dry dimethylformamide, in the presence of a base, e.g. potassium carbonate. Where the ω-R-substituted alkyl halide is the chloride or the bromide, the presence of an alkali metal iodide, e.g. potassium iodide, is advantageous.

The product may be isolated as the free base by addition of water to the cooled reaction mixture, extraction with a suitable organic solvent, e.g. diethyl ether, and vaporati n of the previously washed organic s lution in vacuo to dryness, or alternatively by evaporation of the r acti n mixture in vacuo to dryness, extracti n with a suitable organic solvent, e.g. diethyl ether, removal of undissolved residue from the solution by filtration, washing

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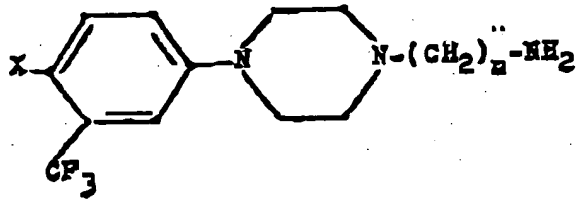
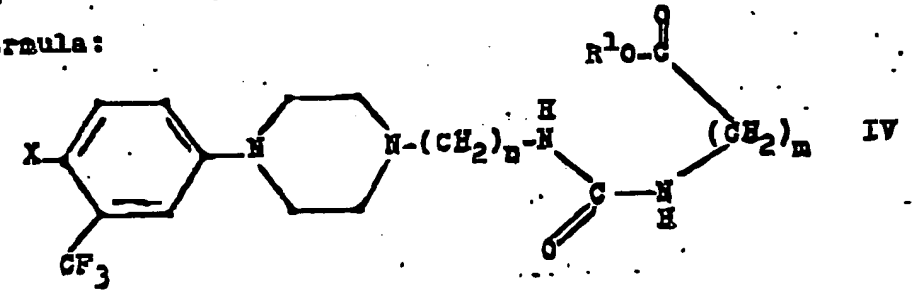
the filtrate with water and evaporation of the rganic solution in vacuo to dryness. Purification of the crude product may then be effected in the usual manner by recrystallization from a suitable solvent, e.g. petrol ether, to yield the free base, or by forming the acid addition salt, e.g. the hydrochloride, by addition of the appropriate acid in a suitable solvent, e.g. diethyl ether, to a solution of the crude base, e.g. in diethyl ether, and collection by filtration and recrystallization of the precipitate from a suitable solvent, e.g. methanol, to produce the pure acid addition salt.

(2) To prepare compounds of the invention in which R of the formula (I) represents the 2,4-dioxo-3-imidazolidinyl or 2,4-dioxo-3-hexahydropyrimidinyl group, an ω-(4-aryl-1-piperazinyl)-alkylamine of the formula:



(III)

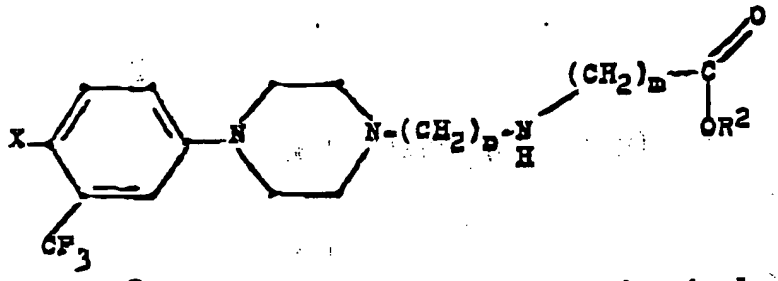
is reacted with a lower alkyl isocyanatoacetate or β-isocyanatopropionate, the lower alkyl group preferably being a methyl or an ethyl group, by heating in a suitable reaction inert organic solvent, e.g. benzene, to produce a compound of the formula:



IV

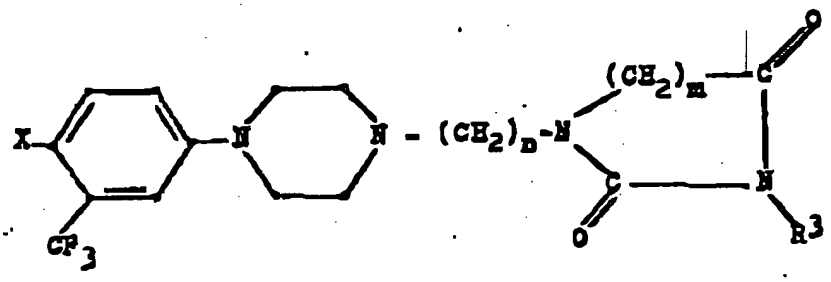
where R^1 represents the lower alkyl group and m is 1 or 2. The product, of the formula (IV), may be isolated by evaporation of the reaction mixture in vacuo and purified by recrystallization of the solid residue, formed if necessary from a gummy residue by trituration in e.g. petrol ether and decantation, from a suitable solvent, e.g. aqueous methanol solution. Ring closure by elimination of the alcohol, R^1OH, to form the compound of the invention is then effected by heating the compound of the formula (IV), for example using as a heating source an oil bath at a temperature of about 200°C., for several hours, and the resultant solid mass is then cooled and purified by recrystallization from a suitable solvent, e.g. a mixture of benzene and petrol ether, and optionally formed into the acid addition salt by conventional means, as described in method (1), which is recrystallized, e.g. from methanol, to purity.

(3) To prepare compounds of the invention in which R of the formula (I) represents a 2,4-dioxo-3-methyl(or ethyl)-1-imidazolidinyl or 2,4-dioxo-3-methyl(or ethyl)-1-hexahydropyrimidinyl group, an amine of the formula (III) is reacted with a lower alkyl haloacetate, hal-CH_2COOR^2, or β-halo-propionate, hal-$CH_2CH_2COOR^2$, in which the lower alkyl group, R^2, and the halogen atom, hal, are preferably a methyl or an ethyl group and a chlorine or a bromine atom, respectively, in a suitable reaction inert organic solvent, e.g. benzene, in the presence of a base, e.g. triethylamine, at room temperature with stirring for several hours. The product, a compound of the formula:



(V)

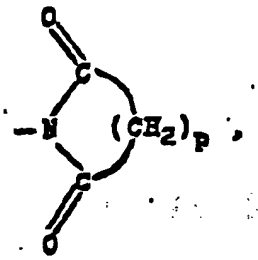
where R^2 is the lower alkyl group and m is 1 or 2, may be isolated by addition of water to the reaction mixture, basification e.g. with sodium hydroxide solution, separation of the organic layer, extraction of the aqueous solution with fresh solvent, e.g. benzene, combination of the organic solution retained and evaporation in vacuo to dryness. The resultant crude free base product may then be used directly in the final stage of the synthesis, or first purified by recrystallization from a suitable solvent. The free base product of the previous stage of the formula (V) is then reacted with methyl (or ethyl) isocyanate, R^3NCO, in a suitable reaction inert organic solvent, e.g. dimethylformamide, at an elevated temperature to produce a compound of the formula:



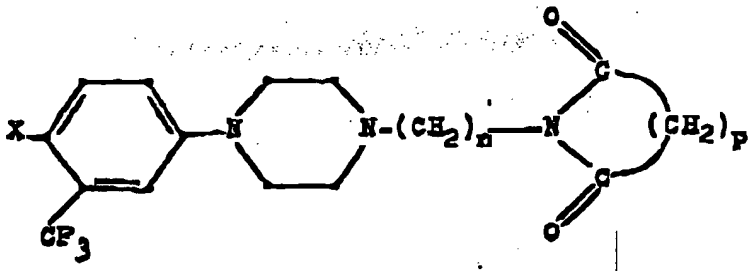
(VI)

which may be isolated by evaporation in vacuo and purified as in method (1).

(4) To prepare compounds of the invention in which R of the formula (I) represents a succinimide or glutarimide group, i.e. a group of the structure:

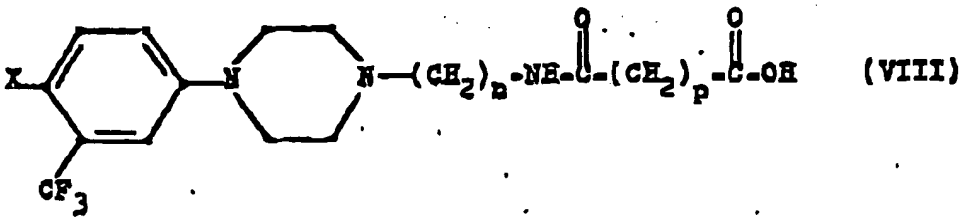


wherein p is 2 or 3, an amine of the formula (III) is reacted with succinic anhydride (p = 2) or glutaric anhydride (p = 3) either in solution in a suitable dry reaction inert organic solvent, e.g. dry pyridine, at an elevated temperature or in the absence of a solvent at an elevated temperature, e.g. at about 200°C. using an oil bath as a heating source, to effect the elimination of water between the reagents with production of the compound of the invention of the formula:



(VII)

The product may be isolated and purified by initial removal of solvent, if used, by evaporation in vacuo and in both cases recrystallization of the reaction residue. If desired, an acid addition salt may then be prepared and purified in the conventional manner. A by-product of the reaction, the corresponding succinic or glutaric half-amide of the formula:



(VIII)

the presence of which can be detected by examination of the infrared absorption spectrum of the crude reaction product, may be formed, and in such a case it may be converted to the desired product of the formula (VII) by heating in boiling acetic anhydride, after which the solvent is removed by evaporation in vacuo and the residue purified as before.

The compound of the formula (III), used as a starting material in Methods (2) to (4), in which X represents a hydrogen atom and n is 2, is disclosed in First Addition No. 93884 to French Patent 1,537,901. That particular compound and others of the formula (III) in which X and n are as hereinbefore defined may be prepared by the method described therein or analogous methods, by reacting unsubstituted or the appropriate halo-substituted 1-(3-trifluoromethylphenyl)piperazine with chloracetonitrile and reducing the product.

Alternatively 1-(3-trifluoromethylphenyl)piperazine or its halo-substituted derivative may be reacted with either chloracetamide or β-chloropropionamide, under reflux conditions in a reaction-inert organic solvent, e.g. ethanol and in the presence of a base, e.g. triethylamine, and the isolated product reduced to the desired 1-aryl-4-(ω-aminoalkyl)piperazine of the formula (III) by use of, for example, sodium dihydro-bis[2-methoxyethoxy] aluminate in benzene solution.

As a third alternative, the appropriate 1-arylpiperazine may be reacted with ω-bromo-ethylamine or -propylamine as its hydrobromide salt under reflux conditions in a reaction-inert organic solvent, e.g. ethanol and in the

presence of a base, e.g. sodium bicarbonate, and the product of the formula (III) isolated from the reaction mixture.

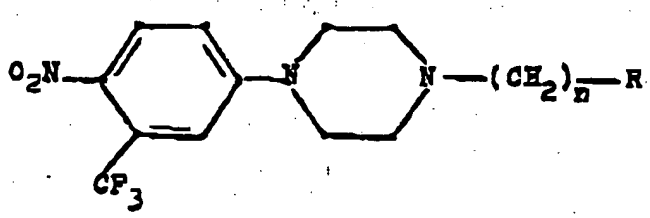
(5) Compounds of the invention in which X of the formula (I) represents a halogen substituent are prepared from compounds of the formula (I) in which X represents a hydrogen atom by appropriate nuclear aromatic halogenation using techniques well-known in the art.

(6) To prepare compounds of the invention in which X of the formula (I) represents a chlorine or a bromine atom, a compound of the formula (I) in which X represents a hydrogen atom is nitrosated such that the nitroso group is incorporated at the 4-position of the 3-trifluoromethylphenyl group, the nitroso group is reduced to an amino group, and the amino-substituted compound is submitted to diazotization followed by the Sandmeyer reaction, using cuprous chloride or bromide, respectively, to yield the required chloro- or bromo-substituted final product. The nitrosation reaction is suitably performed by slowly adding an aqueous solution of sodium nitrite to a solution of the starting compound as a salt, e.g. the hydrochloride, in concentrated hydrochloric acid with vigorous stirring, the initial temperature of the mixture being kept low, e.g. at about -5°C. Generally a thick suspension will form, and the solid therefrom may be collected by filtration and used directly in the next stage. Reduction of the 4-nitroso-3-trifluoromethylphenyl compound to the corresponding 4-amino-substituted compound is suitably effected by heating with tin and dilute hydrochloric acid under reflux conditions for several hours, although several other reductive methods are possible, e.g. using iron or zinc with hydrochloric or acetic acid, zinc or titanium

chloride with hydrochloric acid, and hydrogenation in the presence of such catalysts as Raney nickel, platinum or platinum oxide at room temperature and atmospheric or somewhat higher pressure. The product is isolated by removing sediment from the cooled reaction mixture, basifying the solution, e.g. by addition of aqueous sodium hydroxide solution, and extracting the product into an organic solvent, e.g. diethyl ether, and finally evaporating the solution in vacuo to dryness. Purification of the product may be effected by recrystallization if desired, or the crude product may be used directly in the next stage. Diazotization is conveniently performed by slowly adding an aqueous solution of sodium nitrite portionwise to a cooled solution of the amino compound in hydrochloric or sulphuric acid until it has been established, e.g. by a positive test with starch-iodide indicator paper, that excess nitrous acid is present. The resulting solution of the diazonium chloride or sulphate, respectively, may then be used as such in the subsequent Sandmeyer reaction. For the preparation of the chloro compound by the Sandmeyer procedure, a solution of one equivalent of cuprous chloride in hydrochloric acid is added to the ice-cold diazotization reaction solution, the diazotization in this case having been performed using hydrochloric acid. The sparingly soluble complex which separates is decomposed by warming the mixture, nitogen thereby being evolved, and thereafter the product is suitably isolated by dilution of the solution with water, extraction into a suitable organic solvent, e.g. di thyl ether, evaporation f the organic solution in vacuo t dryness and r crystallization of the solid residue to purity.

Optionally a desired acid addition salt may be prepared by conventional techniques. The bromo compound may be prepared by a similar procedure, but starting from a sulphuric acid diazotization reaction solution and a solution of cuprous bromide in hydrobromic acid.

(7) Compounds of the invention in which X of the formula (I) represents a chlorine or a bromine atom may also be prepared from compounds of the formula:

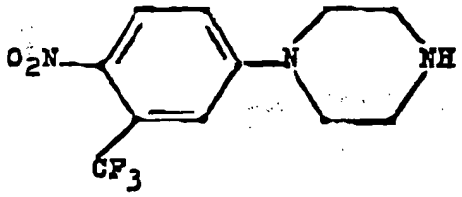


(IX)

by reduction of the nitro group to an amino group under conditions similar to those described for the reduction of the nitroso group to an amino group in Method (6), followed by diazotization and the Sandmeyer reaction to effect the conversion of the amino group to a 4-chloro- or 4-bromo-substituent, as also described in Method (6). The starting compound of the formula (IX) is conveniently prepared by one of the three following methods:

(a) A compound of the formula (I) in which X represents a hydrogen atom is nitrated with a nitrating mixture comprising concentrated nitric and sulphuric acids, and the required 4-nitro-3-trifluoromethylphenyl compound is separated if necessary from other nitrated derivatives, e.g. by fractional crystallization.

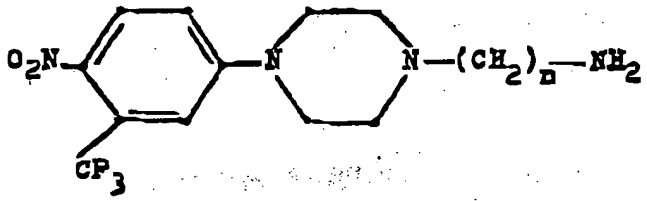
(b) A 1-aryl-piperazine of the formula:



(X)

is reacted with an ω-R-substituted alkyl halide of the formula: hal-$(CH_2)_n$-R, where hal represents the halogen atom, preferably a chlorine or a bromine atom according to the conditions as hereinbefore described in Method (1).

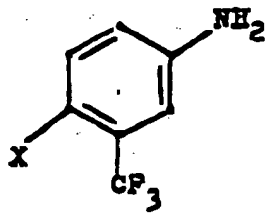
(c) An ω-(4-aryl-1-piperazinyl)-alkylamine of the formula:



(XI)

(prepared by analogous methods to those hereinbefore described for the preparation of compounds of the formula (III)) is submitted to any of the preparative procedures of Methods (2), (3) and (4) as described for the corresponding des-nitro compound of the formula (III).

(8) All the compounds of the invention may be prepared by reacting an aniline derivative of the formula:

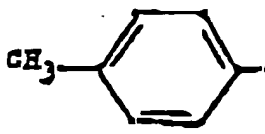


(XII)

with a compound of the formula: Y-$(CH_2)_2$-Z_2N-$(CH_2)_n$-R, in which Y represents a hydroxyl group or a halogen atom, preferably a chlorine atom, in a suitable reaction inert organic solvent, e.g. benzene, in the presence f an acid or base according to whether Y is a hydroxyl group or a halogen atom, respectively. Alternatively, for the prepara-

tion of compounds of the invention of the formula (I) in which X represents a chlorine or a bromine atom, a starting material of the formula (XII) with X replaced by a nitro group may be utilized, and the product of the formula (IX) may be converted to the required final product by means of the procedure indicated in Method (7), as described in greater detail in Method (6). The starting material of the formula: $HO(CH_2)_2\text{-}NH\text{-}(CH_2)_n\text{-}R$ is conveniently prepared by reacting diethanolamine with an ω-R-substituted alkyl halide of the formula: $hal\text{-}(CH_2)_n\text{-}R$, where hal represents a halogen atom, preferably a chlorine or a bromine atom, under conditions similar to those described in Method (1) for the reaction of such a compound with a 1-aryl-piperazine of the formula (II). The product, a compound of the formula: $HO(CH_2)_2\text{-}N(CH_2)_2\text{-}NH\text{-}(CH_2)_n\text{-}R$, may optionally then be converted to the compound of the formula: $hal(CH_2)_2\text{-}N(CH_2)_2\text{-}NH\text{-}(CH_2)_n\text{-}R$ by conventional techniques for the convertion of a primary hydroxyl group to a halogen atom.

(9) As a variation on Method (1) hereinbefore described, the ω-R-substituted alkyl halide, $hal\text{-}(CH_2)_n\text{-}R$, may be replaced by the tosylate of ω-R-substituted alkanol, of the formula:



(XIII)

and this may be reacted with a 1-aryl-piperazine of the formula (I) under similar conditions.

Preparation of the compound of formula II in which X is hydrogen, and compounds of formula II in which X is halogen, which are used as starting materials for methods (1)

and (9), is described in British Patent Specification No. 948,767 (United States Patent Specification No. 3,170,926) and in United States Patent Specification No. 3,637,705, respectively.

The preparation of compounds of the present invention is described in the following Examples, in which all temperatures are given in °C.

EXAMPLE I

1-(3-Trifluoromethylphenyl)piperazine (11.5 g) was added to a mixture of 2-succinimidoethyl chloride (8.1 g), anhydrous potassium carbonate (7.0 g) and potassium iodide (2.0 g) in dry dimethylformamide (50 ml). The mixture was then heated to 100° and maintained at that temperature for 24 hours, after which it was cooled and poured into water (250 ml). The aqueous solution was extracted with diethyl ether (3 x 100 ml) and the organic layers combined, washed with water and evaporated *in vacuo* to give a brown oil which subsequently crystallized. Recrystallization from 80-100° petrol ether afforded a cleaner crystalline product from which the hydrochloride salt was prepared by addition of ethereal hydrogen chloride solution to an ethereal solution of the free base and collection by filtration of the resultant precipitate. The salt was recrystallized from a mixture of methanol and 2-butanone to yield 9.1 g of pure 1-(2-succinimidoethyl)-4-(3-trifluoromethylphenyl)piperazine hydrochloride as white crystals, m.p. 239-241°.

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Analysis:

Found: C, 51.9; H, 5.5; N, 10.7%

Required for $C_{17}H_{20}F_3N_3O_2.HCl$: C, 52.1; H, 5.4; N, 10.7%

EXAMPLES II and III

By methods similar to that of Example I, the compounds shown in the following table were prepared from 1-(3-trifluoromethylphenyl)piperazine and the appropriate ω-cyclic-amido-alkyl chloride.

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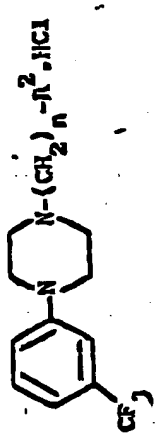
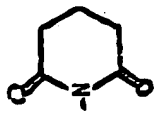


Example	R^2	n	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
XI		3	233-5°	51.1 (51.2	5.5 5.9	10.0 9.9)
XII		2	195-200°	52.7 (53.0	5.9 5.7	9.7 10.3)

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EXAMPLE IV

To a solution of 1-(2-aminoethyl)-4-(3-trifluoromethyl phenyl)piperazine (5.5 g) in benzene (50 ml) was added ethyl isocyanatoacetate (2.6 g) and the mixture was refluxed for one hour, allowed to stand at room temperature overnight and evaporated to dryness in vacuo. The residual gummy solid was triturated in 40-60° petrol ether, the solvent decanted and the solid recrystallized from aqueous methanol solution to afford 1-[2-(3-{ethoxycarbonylmethyl} ureido)ethyl]-4-(3-trifluoromethylphenyl)-piperazine (7.1 g) as white crystals, m.p. 126-8°.

Analysis:

Found: C, 54.0; H, 6.3; N,14.0%

Required for $C_{18}H_{25}F_3N_4O_3$: C, 53.7; H, 6.25; N, 13.9%

The product of the previous stage (5.3 g) was heated in an oil bath to a temperature of 180° and kept at that temperature for 2 hours. The resultant glassy solid was cooled and recrystallized from a mixture of benzene and petrol ether to give a cream-coloured solid. Formation of the hydrochloride salt of the product was effected in the usual manner and this was recrystallized from methanol to yield 3.3 g of 1-[2-(2,4-dioxo-3-imidazolidinyl)ethyl]-4-(3-trifluoromethylphenyl)piperazine hydrochloride, m.p. 300-310°.

Analysis:

Found: C, 49.2; H, 5.1; N, 14.1%

Required for $C_{16}H_{19}F_3N_4O_2.HCl$: C, 48.9; H, 5.1; N, 14.3%

EXAMPLE V

T a stirred mixture of 1-(2-aminoethyl)-4-(3-trifluoromethylphenyl)piperazine (5.46 g) and triethylamine

(4.04 g) in benzene (70 ml) was added ethyl bromoacetate (3.34 g) whereupon precipitation of white solid occurred. Stirring at room temperature was continued for 14½ hours, after which water was added, the aqueous layer basified by addition of aqueous sodium hydroxide solution, and the benzene layer separated from the aqueous layer. The latter was extracted with fresh benzene, and the combined benzene solutions evaporated in vacuo to yield a colourless oil (7.2 g).

A portion of the oil was converted to the hydrochloride salt of the product by conventional means which was recrystallized in turn from mixtures of methanol and isopropanol, methanol and 2-butanone and from ethanol to afford 1-[2-(ethoxycarbonylmethyl)aminoethyl]-4-(3-trifluoromethylphenyl)piperazine dihydrochloride, m.p. 199-201° as white crystals.

Analysis:

Found:	C, 46.6;	H, 6.4;	N, 9.7%
Required for $C_{17}H_{24}F_3N_3O_2.2HCl$:	C, 47.2;	H, 6.1;	N, 9.7%

A mixture of the crude free base product of the previous stage (5.39 g) and methyl isocyanate (1.2 g) in dimethylformamide (50 ml) was stirred at 60° for 6 hours. The mixture was then cooled and water added, whereupon an oil partially separated. Attempts to dissolve the oil in a reasonable quantity of chloroform failed and so the whole was evaporated in vacuo to an oil from which the hydrochloride salt was formed in the usual manner. The salt was recrystallized in turn from ethyl acetate containing a trac of methanol and from a mixture of isopr panol and methan l t yield 1.5 g of 1-[2-(2,4-dioxo-3-methyl-1-imidazolidinyl)-

ethyl7-4-(3-trifluoromethylphenyl)piperazin hydr chloride as white needles, m.p. 231-2°.

Analysis:

Found: C, 50.37; H, 5.37; N, 13.62%

Required for $C_{17}H_{21}F_3N_4O_2.HCl$: C, 50.31; H, 5.22; N, 13.8%

EXAMPLE VI

1-(4-Chloro-3-trifluoromethylphenyl)piperazine (5.0 g) was added to a mixture of 2-succinimidoethyl chloride (3.9 g), anhydrous potassium carbonate (2.65 g) and potassium iodide (0.75 g) in dry dimethylformamide (50 ml), and the mixture heated to 100°C. at which it was maintained for 19 hours. The solution was thereafter cooled, poured into water (250 ml) and the aqueous solution extracted with diethyl ether (3 x 100 ml), the organic layers then being combined, washed with water and evaporated *in vacuo* to afford an oil which subsequently crystallized. Recrystallization from 80-100° petroleum ether afforded pale yellow crystals from which the hydrochloride salt was prepared by addition of ethereal hydrogen chloride solution to an ethereal solution of the free base and collection of the resultant precipitate by filtration. The salt was recrystallized from a mixture of methanol and 2-butanone to yield 1.8 g of pure 1-(4-chloro-3-trifluoromethylphenyl)-4-(2-succinimidoethyl)piperazine hydrochloride, m.p. 256-7°.

Analysis:

Found: C, 48.1; H, 4.7; N, 9.7%

Required for $C_{17}H_{19}ClF_3N_3O_2.HCl$: C, 47.9; H, 4.7; N, 9.8%

EXAMPLES VII and VIII

By methods similar to that described in Example I, the compounds shown in the following Table were prepared

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from 1-(4-halo-3-trifluor methylphenyl)piperazine and the appropriate ω-cyclic-amidoalkyl chloride.

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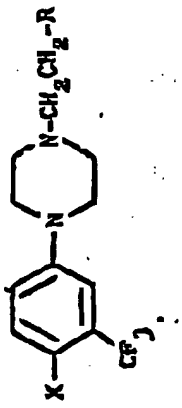
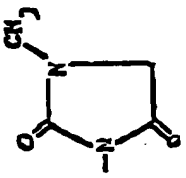
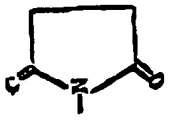


Example	X	R	m.p. °C and free base/salt form	Analysis % (Theoretical in brackets) C	H	N
VII	Cl		227-8° (dihydrochloride)	42.5 (42.75	4.6 4.64	12.0 11.7)
VIII	Br		122-3° (free base)	47.02 (47.00	4.39 4.37	10.14 9.67)

EXAMPLE IX

To a stirred solution of 1-(2-aminoethyl)-4-(3-trifluoromethylphenyl)piperazine (2.73 g) in 50% aqueous acetic acid (50 ml) at room temperature was added dropwise a solution of bromine (1.75 g) in 50% aqueous acetic acid (15 ml). Within 5 minutes from completion of bromine addition the solution had turned colourless from its initial red colour. Stirring at room temperature was continued for a further ½ hour, and thereafter the solution was allowed to stand for one week.

The solution was then evaporated *in vacuo* to remove solvent, and the crude product basified by addition of aqueous sodium hydroxide solution, the whole then being extracted with diethyl ether several times. The ethereal extracts were combined, dried over anhydrous sodium sulphate and evaporated *in vacuo* to an oil (about 3.5 g).

By a conventional technique, the hydrochloride salt of the product was prepared from the oil, and recrystallized from methanol to afford 2.0 g of 1-(2-aminoethyl)-4-(4-bromo-3-trifluoromethylphenyl)piperazine, m.p. 226-8° with decomposition.

Analysis:

Found: C, 34.02; H, 4.52; N, 9.00%

Required for $C_{13}H_{17}BrF_3N_3.3HCl$: C, 33.83; H, 4.37; N, 9.10%

A mixture of the amine product of the previous stage (3.3 g, free base, isolated from the hydrochloride salt by basification) and succinic anhydrid (0.94 g) was heated by means of an oil bath to 190° and then allowed to cool to room temperature. During the heating, evolution of gas was observed, and the oil reaction mixture

darkened. The crude product was crystallized once from absolute ethanol to afford two crops (0.9 g and 0.4 g) of crystalline product, m.p. 123-123.5° for the first crop.

A mixed melting point of 123.5-124° was observed for the mixture of this product (first crop) with the product of Example VIII, and comparison of infrared spectra established its identity with the product of Example VIII.

The compounds of the invention have been found to be potent anorectic agents with advantages over those currently in use.

This has been shown in tests in which their anorectic effect has been measured in rats. In one of such tests the appetite for peeled potatoes of a group of rats starved for 18 hours before oral administration of 10 mg/kg of the test compound (as the free base) and then allowed access to the potatoes half an hour later, measured after periods of 2 hours and 5 hours from the time of presentation of their diet, was compared with the appetite of a second group of control rats which had been subjected to the same diet restrictions but to which only the vehicle for the test compound was administered, usually distilled water. The first group showed a considerably reduced intake of potato compared with the second (control) group after 2 hours, a situation not reversed during the final 3 hours. The 2 hour result demonstrated the presence of anorectic activity of the particular test compound administered whilst the 5 hour result demonstrated its duration of activity. In a second, similar test, various doses were administered in order to calculate one which caus d the reduction of food intake by 50% compared with that of

the controls at 2 hours (ED_{50} 2 hours) and one producing this effect at 5 hours (ED_{50} 5 hours). A comparison between the ED_{50} values at 2 and 5 hours, as in the primary screen previously described, gave an indication of the duration of action of the test compound.

In order to show the absence or otherwise of central nervous system stimulation or sedation, rats were given the test compound orally 2 hours before being placed individually in compartments of an activity recorder and their locomotor activity was measured by counting electronically the interruptions of 2 narrow light beams passing between sources and photoelectric cells along the bottom of each compartment over a period of ten minutes. The average result for 12 animals was compared with that for control animals in the same time period. Dosages were varied in order to calculate that required to increase or decrease by 50% the locomotor activity compared with the value obtained using control animals (ED_{50} 2 hours). The ED_{50} (2 hours) values for anorexia and locomotor activity were then compared, a ratio $\frac{ED_{50} \text{ locomotor activity}}{ED_{50} \text{ anorexia}}$ (each at 2 hours)

greater than 12 being taken to indicate a selective anorectic effect unassociated with any central nervous system excitation or depressant effect of the test compound. Little drug tolerance was shown by the rats to the compounds administered at a rate of 10 mg/kg/day over a period of several weeks in that anorectic activity was maintained at a high level over the period after only a slight decrease during the first week of treatment.

The results of such testing have shown that compounds having the formula (I) where n is 2 and those having the formula (I) where R represents a succinimido group constitute preferred classes of compounds. Compounds of the invention having both such features in the formula (I) are particularly prefarred. Amongst the very best compounds of the invention are 1-(2-succinimidoethyl)-4-(3-trifluoromethylphenyl)piperazine and 1-(2-succinimidoethyl)-4-(4-chloro-3-trifluoromethylphenyl)-piperazine, i.e. the compounds of Examples I and VI, respectively, hereinafter described. The first compound has been found to be embryotopic and teratogenic in tests in pregnant rats and mice but not in rabbits. The second compound has been found to be embryotopic and teratogenic in pregnant rats.

The compounds of the invention can be administered alone, but will generally be administered in admixture with non-toxic carrier or diluent selected with regard to the intended route of administration and comparable with standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

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For administration to a human subject for the purpose of combatting a tendency towards obesity by reducing the appetite, it is expected that oral dosages of the compounds of the invention will be in the range from 0.01 to 10 mg/kg/day, more probably 0.1 to 1, given in a single

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dose or in divided doses. Thus, for typical adult patients, weighing from 50 to 80 kg, individual tablets or capsules, for administration once a day, or up to 4 times a day, could contain from 1 to 200 mg, more probably 5 to 80 mg, of active constituent in a suitable vehicle or carrier. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with age, the weight and response of that patient.

Suitable capsule dosage forms of compounds according to the invention are illustrated by the following Example:

EXAMPLE X

The product of Example I, 1-(2-succinimidoethyl)-4-(3-trifluoromethylphenyl)piperazine hydrochloride, was converted to the free base and formulation of capsules of this compound was then effected using the following constituents:

Capsule (A)	mg/capsule
1-(2-succinimidoethyl)-4-(3-trifluoromethylphenyl)piperazine (free base, active constituent)	5
Maize starch	110
Lactose	225
Lubricant (9 parts magnesium stearate to 1 part sodium lauryl sulphate)	8
Total weight of constituents	348

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Capsule (B)	mg/capsule
1-(2-succinimidoethyl)-4-(3-trifluoromethyl-phenyl)piperazine (free base, active constituent)	20
Maize starch	110
Lactose	250
Lubricant (9:1 magnesium stearate: sodium lauryl sulphate)	8
Total weight of constituents	388

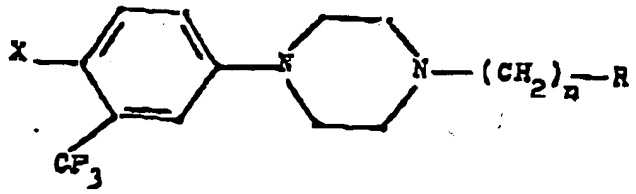
Capsule (C)	
1-(2-succinimidoethyl)-4-(3-trifluoromethylphenyl) piperazine (free base, active constituent)	40
Maize starch	100
Lactose	200
Lubricant (9:1 magnesium stearate: sodium lauryl sulphate)	8
Total weight of constituents	348

In each case the active constituent was blended with the maize starch, lactose and half the lubricant (the latter having been screened through a 60 mesh screen), and the mixture was compressed to a granular state passable through a 30 mesh screen.

The rest of the lubricant was then blended in and the mixture was filled into hard gelatin capsules of suitable size.

The claims defining the invention are as follows:

1. Compounds having the formula:



where R represents a succinimide, glutarimido, 2,4-dioxo-1 (or 3)-imidazolidinyl or 2,4-dioxo-1 (or 3)-hexahydro-pyrimidinyl group, the last two groups being optionally substituted on the imino nitrogen atom with a methyl or an ethyl group;
X represents a hydrogen, fluorine, chlorine or bromine atom;
and n is 2 or 3;
and their non-toxic acid addition salts.

2. Compounds as claimed in claim 1, in which X represents a hydrogen atom.

3. Compounds as claimed in claim 1, in which X represents a fluorine, chlorine or bromine atom.

4. Compounds as claimed in any preceding claim, in which n is 2.

5. Compounds as claimed in any preceding claim, in which R represents a succinimido group.

6. 1-(2-succinimidoethyl)-4-(3-trifluoromethylphenyl)-piperazine and its non-toxic acid addition salts.

7. 1-(2-succinimidoethyl)-4-(4-chloro-3-trifluoromethylphenyl) piperazine and its non-toxic acid addition salts.

8. A compound as claimed in any preceding claim the

preparation of which is described in any one of the Examples.

9. A composition comprising a compound as claimed in any preceding claim in admixture with a non-toxic carrier or diluent.

10. A tablet or capsule containing from 5 to 80 mg of a compound as claimed in any of claims 1 to 8 in admixture with a non-toxic carrier material.

11. A method of reducing appetite in a human subject, and thereby combatting a tendency towards obesity, comprising administering to a human subject an effective amount of a compound as claimed in any of claims 1 to 8.

12. A method as claimed in claim 11, comprising administering from .01 to 10 mg of the compound per kg weight of the subject per day.

13. A method as claimed in claim 12, comprising administering from 0.1 to 1 mg of the compound per kg weight of the subject per day.

DATED this TWENTY-THIRD day of AUGUST, 1972

PFIZER CORPORATION

Patent Attorneys for the Applicant
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(54) Title: ORAL-ADMINISTRATION FORMS OF A MEDICAMENT CONTAINING PANTOPRAZOL

(54) Bezeichnung: PANTOPRAZOL ENTHALTENDE ORALE DARREICHUNGSFORMEN

(57) Abstract

The invention concerns oral-administration forms for pantoprazol, consisting of a core, an intermediate layer and a gastric juice resistant outer layer.

(57) Zusammenfassung

Die Erfindung betrifft orale Darreichungsformen für Pantoprazol, die aus einem Kern, einer Zwischenschicht und einer magensaftresistenten äußeren Schicht bestehen.

VERIFIED TRANSLATION OF PCT

Verification of Translation

In the matter of an Australian
Patent Application corresponding
to the International Application
PCT/EP92/01341

I, Dr. Ulrich Wolf, Im Grün 7b, D-78465 Konstanz, Federal Republic of Germany, am conversant with the English and German languages, and I state that the following is a true and correct translation of the PCT Application filed under

No.	PCT/EP92/01341	by	Byk Gulden Lomberg Chemische Fabrik GmbH
at	European Patent Office, Munich, Federal Republic of Germany	on	13.06.1992

for Oral-administration forms of a medicament containing pantoprazol

Konstanz, the 09th day of November, 1993

Dr. Ulrich Wolf

ORAL ADMINISTRATION FORMS OF A MEDICAMENT CONTAINING PANTOPRAZOL

Prior art

European Patent Application EP-A-244 380 describes oral presentation forms for acid-unstable active compounds from the class of H^+/K^+-ATPase inhibitors having a pyridylmethylsulphinyl-1H-benzimidazole structure, which have a core, an intermediate layer, and an outer layer which is resistant to gastric juice. European Patent Application EP-A-247 983 describes and claims the formulations disclosed in EP-A-244 380 in connection with the H^+/K^+-ATPase inhibitor omeprazole.

In the case of the presentation forms claimed in European Patent Applications EP-A-244 380 and EP-A-247 983, stabilization of the acid-unstable active compounds is achieved, in particular, by adding bases to the core and thus increasing the pH; to achieve an adequate storage stability, however, certain conditions must be maintained both during preparation and during storage, and these can be reconciled with an optimum pharmaceutical formulation and problem-free stock-holding only with difficulty. EP-A-247 983 thus appropriately states: "It is essential for long-term stability during storage that the water content of the presentation form containing the active compound omeprazole (tablets, capsules and pellets with a coating which is resistant to gastric juice) is kept low and is preferably not more that 1.5 wt.%. Final packs with pellets which have a coating which is resistant to gastric juice and are contained in hard gelatine capsules accordingly are preferably to be provided with drying agents which reduce the water content of the gelatine shells to the extent that the water content in the pellets does not exceed 1.5 wt.%".

The water content, which is to be kept low during preparation of pellet cores for stability reasons, thus means that the mass to be extruded for preparation of the pellet core is no longer sufficiently plastic for the extrudate subsequently to be rounded off into spherical particles. Rather, cylindrical bodies are formed, which, during the subsequent coating step, receive thinner lacquer coatings on the ends and therefore do not have the required resistance to gastric juice at these points, and moreover do not protect the core reliably from the coating which is resistant to gastric juice by a sub-coating, which is essential for the stability.

The stability problems described also arise if attempts are made to formulate the H^+/K^+-ATPase inhibitor pantoprazole (prop. INN for the compound 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole) as described in European Patent Applications EP-A-244 380 and EP-A-247 983.

Description of the invention

It has now been found, surprisingly, that if certain fillers and binders often used as tablet auxiliaries, such as are mentioned for the preparation of the pellet and tablet cores in European Patent Applications EP-A-244 380 and EP-A-247 983, are dispensed with, the stability problems described do not occur. These fillers and binders are, in particular, lactose, microcrystalline cellulose and hydroxypropylcellulose.

The invention thus relates to a medicament in pellet or tablet form which contains the active compound pantoprazole, is to be administered orally, is resistant to gastric juice and consists of a basic pellet core or tablet core, one or more inert, water-soluble intermediate layer(s) and an outer layer which is resistant to gastric juice, and which is characterized in that the core contains, in addition to pantoprazole or in addition to a pantoprazole salt, polyvinylpyrrolidone and/or hydroxypropylmethylcellulose as the binder, and if desired mannitol additionally as an inert filler.

For a basic reaction of the pellet core or tablet core - if the desired increase in pH has not already been achieved by using the active compound salt - an inorganic base is admixed to this. Examples which may be mentioned here are the pharmacologically tolerated alkali metal, alkaline earth metal or earth metal salts of weak acids and the pharmacologically tolerated hydroxides and oxides of alkaline earth and earth metals. Sodium carbonate may be mentioned as an example of a base which is to be singled out.

In addition to the filler and binder, other auxiliaries, in particular lubricants and release agents, as well as tablet-disintegrating agents, are also employed in the preparation of the tablet cores.

Examples of lubricants and release agents which may be mentioned are the calcium salts of higher fatty acids, such as e.g. calcium stearate.

Possible tablet-disintegrating agents are, in particular, chemically inert agents. (Transversely) crosslinked polyvinylpyrrolidone (e.g. Crospovidone) may be mentioned as a preferred tablet-disintegrating agent.

In respect of the water-soluble intermediate layer(s) to be applied to the pellet core or tablet core, reference may be made to those water-soluble layers such as are usually used before application of layers which are resistant to gastric juice, or such as are described e.g. in DE-OS 39 01 151. Examples which may be mentioned of film polymers which can be used for the intermediate layer are hydroxypropylmethylcellulose and/or polyvinylpyrrolidone, to which plasticizers (such as, for example, propylene glycol) and/or other additives and auxiliaries (e.g. buffers, bases or pigments) can also be added if desired.

The expert knows, on the basis of his technical knowledge, what outer layers which are resistant to gastric juice can be used. Aqueous dispersions of suitable polymers which are resistant to gastric juice, such as, for example, a methacrylic acid/methyl methacrylate copolymer, if desired with the addition of a plasticizer (e.g. triethyl acetate), are advantageously used (to avoid organic solvents and since the core according to the invention does not have the sensitivity to water known from the prior art).

The active compound pantoprazole is known from European Patent 166 287. Examples of salts of pantoprazole which may be mentioned are the salts mentioned in European Patent 166 287. The sodium salt is a preferred salt.

The use of mannitol as the sole filler for tablets requires a suitable binder, which must impart an adequate hardness to the core. The polyvinylpyrrolidone used as a binder for preparation of the core is, in particular, a product of higher molecular weight (about 300,000 to 400,000). PVP 90 (molecular weight about 360,000) may be mentioned as a preferred polyvinylpyrrolidone.

Compared with the presentation forms known from the prior art for other H^+/K^+-ATPase inhibitors having the pyridylmethylsulphinyl-1H-benzimidazole structure, the oral presentation form according to the invention is

distinguished, in particular, in that a water content in the tablet core in excess of 1.5 wt.% does not lead to discoloration (decomposition) of the active compound. Stable tablets are thus obtained even with a relatively high residual moisture content (of e.g. 5 to 8 wt.%) in the granules.

Pellets can be obtained by application of a preliminary isolation to sucrose starter pellets and subsequent application of a 30 % solution of the active compound in isopropanol with hydroxymethylpropylcellulose as the binder.

The isolation layer can also be applied, analogously to tablets, using corresponding ready-made dispersions (e.g. Opadry). The coating with a layer which is resistant to gastric juice is carried out by a procedure analogous to that for tablets.

The following formulation examples illustrate the invention in more detail, without limiting it.

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The following formulation examples illustrate the invention in more detail, without limiting it.

Examples

1. Tablets

I. Tablet core

a)	Pantoprazole-Na sesquihydrate	45.1 mg
b)	Sodium carbonate	10.0 mg
c)	Mannitol	42.7 mg
d)	Crospovidone	50.0 mg
e)	PVP 90 (povidone)	4.0 mg
f)	Calcium stearate	3.2 mg
		155.0 mg

a) is mixed with some of b), c) and d). The remainders of b) and c) are added to a clear aqueous solution of e) and the pH is brought to > 10 with b). Granules are obtained with this solution in a fluidized bed. The remainder of d), and f) are added to the dry granules and the granules are pressed on a suitable tablet-making machine.

II. Preliminary isolation (intermediate layer)

g)	HPMC 2910, 3 cps	15.83 mg
h)	PVP 25	0.32 mg
i)	Titanium dioxide	0.20 mg
j)	LB Iron oxide yellow 100 E 172	0.025 mg
k)	Propylene glycol	3.64 mg
		20.00 mg

Total weight per preisolated core 175.00 mg

g) is dissolved in water and h) is added and also dissolved (A). i) and j) are suspended in water using a suitable stirrer (B). A and B are combined. After addition of k), the suspension is sieved immediately before further processing, during which the tablet cores obtained under I. are coated with an adequate layer thickness of the suspension in a suitable apparatus.

III. Coating with a layer which is resistant to gastric juice

l)	Eudragit® L 30 D	13.64 mg
m)	Triethyl citrate	1.36 mg
		15.00 mg
Total weight per film-coated tablet resistant to gastric juice		190.00 mg

l) is diluted with water and m) is added. The dispersion is sieved before processing.

III. is sprayed, in suitable apparatuses, onto the preisolated cores obtained under II.

2. Pellets

I. Starter pellets

a)	Sucrose pellets (0.7-0.85 mm)	950.0 g
b)	Hydroxypropylmethylcellulose	50.0 g

a) is sprayed with an aqueous solution of b) in a fluidized bed (Wurster process).

II. Active pellets

c)	Pantoprazole-Na sesquihydrate	403.0 g
d)	Hydroxypropylmethylcellulose	40.3 g

c) and d) are dissolved in succession in 30 % isopropanol, and the solution is sprayed, in a fluidized bed (Wurster process), onto 900 g of the starter pellets obtained under I.

III. Preliminary isolation (intermediate layer)

The coating operation is carried out by a procedure analogous to that described for the tablets, in a coating pan or in a fluidized bed.

IV. Coating with a layer which is resistant to gastric juice

The coating operation is carried out by a procedure analogous to that described for the tablets, in a coating pan or in a fluidized bed.

Capsules of suitable size (e.g. 1) are then filled with the pellets.

Patent Claims

1. Medicament in pellet or tablet form which is to be administered orally and is resistant to gastric juice, in which the pellets or tablets consist of

- a core in which the active compound or its physiologically tolerated salt is present as a mixture with one or more binders, fillers and if desired other tablet auxiliaries, and if desired one or more basic physiologically tolerated inorganic compounds,
- one or more inert, water-soluble intermediate layers surrounding this core and
- an outer layer which is resistant to gastric juice,

characterized in that, in the core, pantoprazole is used as the active compound, polyvinylpyrrolidone and/or hydroxypropylmethylcellulose is used as the binder and, if desired, mannitol is used as the filler.

2. Medicament according to Claim 1 in tablet form, characterized in that polyvinylpyrrolidone and/or hydroxypropylmethylcellulose is used as the binder and mannitol is used as the filler.

3. Medicament according to Claim 1 in pellet form, characterized in that polyvinylpyrrolidone and/or hydroxypropylmethylcellulose is used as the binder.

4. Medicament according to Claim 1 or 2 or 3, characterized in that pantoprazole-sodium is used as the physiologically tolerated active compound salt.

5. Medicament according to Claim 1 or 2 or 3, characterized in that pharmacologically tolerated alkali metal, alkaline earth metal or earth metal salts of weak acids or pharmacologically tolerated hydroxides or oxides of alkaline earth or earth metals are used as the basic, physiologically tolerated inorganic compounds.

6. Medicaments according to Claim 1 or 2 or 3, characterized in that sodium carbonate is used as the basic, physiologically tolerated inorganic comp und.